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Review article

Human papillomavirus infection and pathogenesis in urothelial cells: A mini-review

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ABSTRACT

Several recent studies described that high-risk human papillomavirus (HPV) infection could have a potential role in the development of malignancies other than cervical cancer, such as laryngeal carcinoma, penile carcinoma, and anal carcinoma. However, the etiological role of HPV infection in the pathogenesis of urinary tract has not been clarified. Many epidemiological studies demonstrated that HPV infections frequently occur in the external genitalia through sexual contact; however, it was reported that HPV infection could also occur in the urinary tract, including the urethra and urinary bladder. Some morphological changes of cells associated with HPV infection and mild atypical cells, suspected to be intraneoplasia, were seen in HPV-positive samples obtained from the urinary tract. Some clinical studies and meta-analysis have indicated that HPV infection is likely to have a certain etiological correlation with the development of bladder carcinoma, although its prevalence may vary according to HPV type, study population, region, histological type, detection methods, and other variables. According to the results of previous studies, the prevalence of HPV greatly widely varies in cases of bladder carcinoma. Further research by case–control or large-scales studies is thus required to reach a more definite conclusion.

1. Introduction

Sexually transmitted human papillomavirus (HPV) infection has been identified as a cause of cervical cancer, and it is now widely recognized as responsible for more than 95% of cervical cancer cases. Since the discovery of HPV 16 and 18 DNA in cervical cancer tissue by zur Hausen's group [1], more than 100 types of HPV have been isolated, and at least 15 types of high-risk HPV types have been identified often in association with cervical cancer. HPV infection in the cervix generally occurs in over 50% of young women within a few years of sexual intercourse initiation, and 70–80% of women are likely to present the infection throughout their lives [2]. Thus, cervical HPV infection is one of the most common sexually transmitted infections (STIs) in women.

Conversely, many epidemiological studies described that the prevalence of HPV among healthy men, who are considered only a HPV reservoir, is as high as that among healthy women [3,4]. In addition, several recent studies described that high-risk HPV infection could have a potential role in the development of other malignancies, such as laryngeal carcinoma, penile cancer, and anal cancer [5–7]. Almost 10% of the cancer burden worldwide has been linked to HPV infection [8]. Thus, a quadrivalent HPV vaccine type 6, 11, 16, 18 (Gardasil®; Merck & Co., Inc, North Carolina, USA.) has been developed and made available for men in over 70 countries worldwide.

However, the etiological role of HPV infection in the pathogenesis of urinary tract cancer has not been clarified. In particular, the association of HPV infection with the development of bladder cancer continues to be controversial. To address this, we analyzed some internationally published studies, and reviewed the possibility of pathogenesis of HPV infection in urothelial epithelium.

2. HPV infection in the urothelical epithelium

Although the prevalence of HPV varies on the basis of sampling, processing methods, and/or samples specimens, the frequent anatomic site for HPV infection in men is generally the external

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genitalia, which comes in direct contact with the female genitalia. Further, HPV infection in men is often detected in the glans, corona, prepuce, shaft of the penis, and distal urethra [3,9]. Giuliano et al. examined the presence of HPV-DNA in multiple genital sites of 463 healthy men and reported that HPV was most commonly detected on the penile shaft (49.9%), followed by the glans (35.8%), scrotum (34.2%), perianal area (20.0%), anal canal (17.6%), urethra (10.1%), and semen (5.3%); the HPV detection rate was the poorest in urine samples (0.8%) [9]. Furthermore, Nicolau et al. determined the prevalence of HPV-DNA according to some anatomical sites in 50 male partners of HPV-infected women and found that HPV detection was 44% in the inner prepuce, 30% in the distal urethra, 24% in the glans, 24% in the external prepuce of penile shaft, 12% in the scrotum, and 8% in the anus [10].

However, many previous studies have failed to detect HPV infection in the urinary tract, especially from urine samples. Giuliano et al. found a low HPV infection rate (0.8%) in urine samples collected from 463 healthy men, with the adequacy rate of 51.5% positive for the β-globin gene [9]. Lazcano-Ponce et al. investigated HPV prevalence in samples obtained by rubbing the urethral-coronal sulcus versus that of urine samples among 120 Mexican healthy men, and described that HPV was detected in 42.7% of the samples by rubbing versus 6.9% of the urine samples [11]. A systematic review also reported that the HPV detection rate from urine samples was less than 7% [3], although higher HPV-positive rates were observed in samples obtained by scraping the male external genitalia, which suggests that urine may not be suitable for detection of HPV.

However, the recent development of higher-sensitivity methods using polymerase chain reaction (PCR) for the detection of a wide spectrum HPV types and the improvement of sampling procedures have contributed to a relative higher detection of HPV infection, even in urine samples [4,12–14]. Our previous study demonstrated that HPV infection was detected in 31%, 20%, and 24% of samples obtained from the penis, urethra, and urine, respectively, by using high-sensitivity flow-through hybridization among patients with urethritis [4]. Both urine and urethral samples were counted as being from the same source (the urinary tract), and hence, the prevalence was almost the same between the penis and the urinary tract. Furthermore, Kawaguchi et al. demonstrated that application of liquid-based cytology, which is widely used for uterine and cervical cancer screening in women, is a promising method for molecular analysis of HPV in the urinary tract [12]. The prevalence of HPV in urine samples, detected using liquid-based cytology, was 21% in 136 patients with urethritis and 3.3% in 156 healthy men (control), with adequacy detection rate of β-globin of more than 97% in both groups. In addition, another report described the comparison of the HPV-positive rate between the oral cavity and urine among patients who attended the STD clinic by using same liquid-based cytology procedure, and found that HPV detection rates were 18.8% and 22.1% in oral and urine samples, respectively [13]. Moreover, the detection of HPV in urine samples suggests that HPV could infect any site on the urinary tract, such as the urethra, prostate, and urinary bladder. Since the studies including HPV detection from urine samples using recent improved methods have been limited, further studies are likely to be required.

3. The origin of HPV infection within the urinary tract determined from urinary samples

Among the HPV-positive urine samples, it is important to determine the origin of HPV infection within the urinary tract, such as the distal or proximal urethra, prostate, and urinary bladder. A previous report confirmed the localization of HPV-DNA in urothelial cells, such as urethral squamous cells and bladder urothelial cells by in situ hybridization (ISH) analysis [12]. Further, some studies have reported the occurrence of condyloma acuminata in the urinary bladder [15,16]. A case with high-risk HPV-positive bladder carcinoma that developed after the same high-risk type HPV infection in the urethra has also been reported [17]. These findings suggest that HPV first infects the distal urethra by sexual contact and ascends through the urethra into the urothelial epithelium of the bladder, and thus, HPV infection can be detected in the urothelial cells of the urinary bladder.

Furthermore, some reports demonstrated the presence of some morphological changes of cells related to HPV infection and mild atypical cells, suspected to be intraneoplasia, in HPV-positive samples obtained from the urinary tract [12,18,19]. One study reported that cytological signs of HPV infection and cytological atypia, suspected to indicate urethral intraepithelial neoplasia, were observed in 58% and 33%, of high-risk HPV-positive samples, respectively [18]. A recent study to investigate cytological findings in samples obtained by rubbing the urethral-coronal sulcus of 50 male sexual partners of women with HPV-related cervical disease described that mild koilocytosis and dyskeratosis were observed in 48% and 48% of the cases, respectively [19]. Another study also demonstrated that some morphological changes of cells related to HPV infection were observed in 20.7% of the HPV-positive liquid-based urine samples [12]. HPV infection in the urinary bladder may cause cytological changes of the urothelial epitheliums, similar to those in the HPV infected cervix. These findings suggest that HPV infection may result in the development of tumors in the urinary tract of men after persistent long-term infection.

4. HPV prevalence in bladder carcinoma

Kitamura et al. first reported a HPV 16-positive case among 10 bladder tumors based on Southern blotting analysis in 1988 [20], and suggested a possible etiological role in the development of bladder carcinoma. Excluding the case reports and review articles, 56 subsequent studies have attempted to determine the associations between HPV infection and bladder carcinoma (Table 1) [20–75]. The prevalence of HPV infection in bladder carcinoma varies among reports, and ranges from 0% to 81.3%. Twenty-seven reports suggested a potential correlation between HPV infection and bladder carcinoma, whereas the other reports denied its etiological role in bladder carcinogenesis, with the HPV prevalence rate ranging from 0% to 10%. Therefore, the role of HPV in bladder carcinoma has still not been consensual.

Several explanations for this variability of HPV prevalence in bladder carcinoma have been proposed, including sampling problems, contamination, differences in sensitivity of the detection methods used, and differences among study populations and histological tumor type. The mean sample size in the previous reports was 60 (ranging from 10 to 187), and large population studies, including more than 100 subjects, are limited. Further, there have also been limited studies, including usage of the high-sensitivity PCR method, which can detect a wide spectrum of HPV types. Thus, it is important to investigate a sufficient number of cases by using a standardized microbiological technique to reach more definite conclusions.

5. Comparison of HPV prevalence between bladder carcinoma and non-carcinomatous mucosa

Nineteen previous studies compared HPV-positive rate between bladder carcinoma and non-carcinomatous lesions, such as non-specific cystitis and normal mucosa (Table 2), and the prevalence of HPV varied on the basis of sampling, processing method, or geographic location of study population. Thirteen (68%) studies

Table 1
Details of the previous studies on HPV prevalence of bladder carcinoma.

Author [reference]	Year	Samples	Pathology	*N*	Methods	Analyzed HPV-types	HPV detection (%)	Detected HPV types (number)
Kitamura [20]	1988	Frozen	UC/AD	10	PCR + dot blot	1,2,6,11,16,18	1 (10%)	Type 16 (1)
Bryant [21]	1991	Fixed	UC/AD	100	ISH	6/11, 16/18	12 (12%)	Type 16/18 (12)
Kerleys [22]	1991	Fixed	UC/SCC/AD	27	PCR + ISH	6,11,16,18.31,33,35	1 (3.7%)	Type 11 (1)
Knowles [23]	1992	Frozen	UC/SCC/AD	108	PCR + SBH	1/2,5/6 + 5,8,11,16,18,33	0 (0%)	None
Chetsanga [24]	1992	Frozen	UC	44	PCR + dot blot	Not detailed	1 (2.3%)	Type 16 (1)
Shibutani [25]	1992	Frozen	UC	20	SBH	6/11, 16/18, 31/33	4 (20%)	Type 6/11 (2), type 16/18 (1), type 31/33 (1)
Anwar [26]	1992	Fixed	UC/SCC	48	PCR + dot blot	6,11,16,18,33	39 (81%)	Type 18 (18), type 33 (14), type 16 (13)
Yu ST [27]	1993	Frozen	UC	53	PCR	16, 18	30 (57%)	Type 16 (28), type 18 (2)
Wilczynsky [28]	1993	Frozen	SCC	22	PCR + SBH	6,11,16,18	1 (4.5%)	type 6 (1)
Sinclair [29]	1993	Frozen	UC	14	PCR	GP5+/GP6+, MYO9/11 (not detailed)	0 (0%)	None
Saltzstein [30]	1993	Frozen/fixed	UC	33	PCR + SBH	6,11,16,18,31,33	0 (0%)	None
Furihata [31]	1993	Fixed	UC	90	ISH	16, 18, 33	28 (31%)	None
Mincione [32]	1994	Fixed	UC	18	ISH	6/11, 16/18, 31/33/51	1 (5.6%)	Type 31/33/51 (1)
Chang [33]	1994	Fixed	UC	108	ISH + PCR	6,11,16,18,31,33,35,39,40,45,51,59	0 (0%)	None
Agliano [34]	1994	Fixed	UC	46	PCR + dot blot	16,18	23 (50%)	Type 16 (11), type 18 (7), type 16/18 (7)
Maloney [35]	1994	Fixed	UC/SCC	42	PCR	6/11/13/16/18/31/32/33/35/45/51	1 (4.4%)	Type 18 (1)
Noel [36]	1994	Fixed	UC	75	PCR	6b,11,16,18,33	2 (2.7%)	Type 16 (2)
Kamel [37]	1995	Fixed	UC/SCC	47	ISH	6,11,16,18,31,33	27 (57%)	Type 31 (19), type 18 (16), type 33 (13) Type 16 (10), type 11 (10), type 6 (13)
Sano [38]	1995	Fixed	BT	93	PCR + ISH	Multiple type + ISH16, 18 prove	0 (0%)	None
Kim [39]	1995	Fixed	UC	23	PCR + dot blot	6/11/16/18/31/33	8 (35%)	Type 16 (4), type 18 (8)
Smetana [40]	1995	Frozen	UC	110	ISH + IHC + PCR	Wide-PCR, 6/11,16/18,31/33/35	59 (54%)	Not detailed
LaRue [41]	1995	Frozen	UC	71	PCR/SBH	Wide-PCR; 6,11.16,18,33	28 (39%)	Type 16 (27), type 6/11 (1)
Lopez-Beltran [42]	1995	Fixed	UC	76	PCR/ISH	6,11,16,18 (+31/33/35)	7 (9.2%)	Type 16 (7)
Gopalkrishna [43]	1995	Fixed	UC	10	PCR/ISH	16	1 (10%)	Type 16 (1)
Tenti [44]	1996	Fixed	UC	79	PCR + SBH	6/11, 16,18, 33	26 (33%)	Type 16 (21), type 18 (8)
Lopez-Beltran [45]	1996	Fixed	UC	76	PCR	6, 11, 16, 18	7 (9.2%)	Type 16 (7), type 6 (1)
Mvula [46]	1996	Fixed	UC/SCC	36	PCR	16,18, wide PCR(6/11/31/33/42/52/58)	1 (2.8%)	Type 16 (1)
Lopez-Beltran [47]	1996	Fixed	UC	76	IHC + ISH	6/11, 16/18, 31/33/35	25 (33%)	Type 16/18 (12), UK (13)
Boucher [48]	1996	Fixed	UC/SCC	55	SBH	6/11, 16	0 (0%)	None
Lu [49]	1997	Fixed	UC/SCC/AD	31	ISH	16,18	0 (0%)	None
Cooper [50]	1997	Fixed	SCC	25	PCR + ISH	6,11,16,18,31,33	0 (0%)	None
Chan [51]	1997	Fixed	UC	20	PCR + SBH	6,11,16,18,31,33	6 (30%)	type18 (6)
Aynaud [52]	1998	Frozen	UC	57	PCR + dot blot	6,11,16,18,31,33,35,39,42	0 (0%)	None
Gazzaniga [53]	1998	Frozen	UC	35	PCR + dot blot	16, 18	11 (31%)	Type 16 (6), type 18 (5)
De Gaetani [54]	1999	Fixed	UC	43	ISH	6/11,16/18, 31/33/35	17 (40%)	Type 6/11 (3), type 16/18 (6), type 31/33/35 (10)
Simoneau [55]	1999	Frozen	UC	187	PCR + dot blot	6,11,16,18, 33	16 (8.5%)	Type 16 (6), type 6 (3), type 11 (3)
Tekin [56]	1999	Frozen	UC	42	PCR	16,18	2 (4.8%)	Type 16 (2)
Khaled [57]	2001	Fixed	UC/SCC/AD	50	ISH	16/18	23 (46%)	Type 16/18 (23)
Sur [58]	2001	Fixed	UC	91	PCR + ISH	GP5+/GP6+, prove 6,11,16,18,31,33	1 (1.5%)	None
Westenend [59]	2001	Fixed	SCC	16	ISH	6/11,16/18,31/33/51	0 (0%)	None
Fioriti [60]	2003	Frozen	UC	32	PCR	GP5+/GP6+ (Not detailed)	1 (3%)	Type 6 (1)
Khaled [61]	2003	Fixed	UC/SCC	99	PCR	6,11,16,18,33	48 (49%)	Type 16 (36), type 18 (14), type 6 (3), type 11 (3)
Barghi [62]	2005	Fixed	UC	59	PCR	6,11,16,18,31,33,35	21 (36%)	Type 18 (17), type 6 (4), type 33 (3)
Youshya [63]	2005	Fixed	UC	78	PCR + IHC	GP5+/GP6+ (Not detailed)	0 (0%)	None
Helal [64]	2006	Fixed	UC/SCC	114	ISH	6/11,16/18,31/33	1 (0.9%)	Type 16 (1)
Moonen [65]	2007	Wash	UC	99	PCR	GP5+/GP6+(6,11,18,31,33,39,40,52)	15 (15%)	Type 18 (3), type 16 (2), type 6 (1), type 11 (1) Type 31 (1), type 40 (1), type 52 (1), UK type (1)
Badawi [66]	2008	Frozen	UC/SCC	20	PCR	16,18,52	9 (45%)	Type16 (9), type18 (2)
Ben Selma [67]	2010	Fixed	UC/SCC/AD	125	PCR	6,11,16,18,30,31,33,35,45,51,52,58	0 (0%)	None
Yavuzer [68]	2011	Fixed	UC	70	PCR	6,11,16,18,31,33,35,39,42,43,44,45,51,52,56 58,59,66,68	0 (0%)	None
Shigehara [69]	2011	Frozen/fixed	UC/SCC/AD	117	PCR + ISH + IHC	6,11,16,18,31,33,35,39,42,43,44,45, 51,52,53,56,58,59,66,68,CP8304	18 (15%)	Type16 (6), type18 (4), type33 (3), type 31 (1) Type52 (1), type56 (1), type58(1), UK type (1)
Cai [70]	2011	Frozen	UC	78	PCR	6,11,16,18,26,31,33,35,39,40,43,44,45,51,52 53,54,56,58,59,66,68,69,70,71,73,74,82	27 (35%)	Type 16 (4), type 18 (6), type 31 (3), type 45 (5)
Polesel [71]	2012	frozen	UC	114	PCR	16,18,26,31,33,35,39,45,51,52,53,56,58,59 66,68,70,73,82	7 (6.1%)	Type 56 (2), type 31 (1), type 35 (1), type 45 (1) type 58 (1), type 70 (1)

(*continued on next page*)

Table 1 (*continued*)

Author [reference]	Year	Samples	Pathology	*N*	Methods	Analyzed HPV-types	HPV detection (%)	Detected HPV types (number)
Barghi [72]	2012	Frozen	UC	82	PCR	16/18	24 (29%)	Type 18 (9), type 16 (3), UK type (12)
Steinestel [73]	2013	Fixed	CIS	60	PCR	6,11,16,18,31,33,35,39,45,51,52,53,56,58,59	0 (0%)	None
Berrada [74]	2013	Fixed	UC/SCC	43	PCR	GP5/6, MY09/MY11 (Not detailed)	22 (52%)	Type 18 (21), type 31 (1)
Kim [75]	2014	Fixed	UC	35	PCR	6,11,16,18,31 33,34.35,39,40,43,44,45,51,52 56, 58, 59, 66, 68,34, 70	6 (17%)	Type 18 (6)

HPV, human papillomavirus; UC, urothelial carcinoma; AD, adenocarcinoma; SCC, squamous cell carcinoma; BT, bladder tumor; CIS, carcinoma in situ; PCR, polymerase chain reaction; dot blot, dot blot hybridization; ISH, in situ hybridization; SBH, southern blot hybridization; UK, unknown.

demonstrated that the HPV prevalence (12–81%) in bladder carcinoma was significantly higher compared with that (0–33%) in non-carcinomatous bladder mucosa, and have supported the etiological role of HPV in the development of bladder carcinoma. Many of recent case–control studies are especially likely to suggest a possible correlation with HPV carcinogenesis by using the high-sensitivity PCR method. One previous case–control study reported that HPV-DNA was detected in 18 of 117 (15%) bladder carcinomas and this finding was supported by the presence of HPV-DNA signals by ISH analysis in HPV-positive samples [69]. Alternatively, Cai et al. described that high-risk HPV-DNA in bladder carcinoma was detected in 27 of 78 (34.6%) samples, and was also detected in 36 of 78 (46.1%) urine samples obtained from the patients with bladder carcinoma [70]. Conversely, HPV was detected in six of 59 (10.1%) specimens from patients without cancer, and this study highlights the correlation between urothelial bladder carcinoma and high-risk type HPV infection, suggesting the potential pathogenetic role of high-risk HPV types in urothelial bladder carcinoma development [70].

A recent meta-analysis with 19 case–control studies reported an HPV prevalence of 16.88% (95% CI, 15.53%–18.31%) among the bladder carcinoma cases, most of which were high-risk HPV types, and suggested that infection with high-risk HPV types, especially HPV type 16, may play a role in bladder carcinogenesis [76]. Another meta-analysis, including 21 studies, also found a significant effect between HPV and bladder carcinoma with an odds ratio (OR) of 2.13 (95% CI, 1.54%–2.95%) [77].

HPV infection is likely to have a certain etiological correlation with bladder carcinoma. However, in comparison with the fact that HPV infection is responsible for more than 95% of cervical cancers, the etiological role of HPV infection demonstrates a somewhat minimal relationship in the development of bladder carcinoma.

Table 2
Case-control studies on HPV prevalence in bladder carcinoma.

Author [reference]	Year	Samples	Pathology	*N*	HPV detection
			Control		
Bryant [21]	1991	Fixed	UC	100	12 (12%)
			BPH	8	0 (0%)
Kerleys [22]	1991	Fixed	UC/SCC/AD	27	1 (3.7%)
			Normal	5	0 (0%)
Knowles [23]	1992	Frozen	UC/SCC/AD	108	0 (0%)
			cystitis	3	0 (0%)
Anwar [26]	1992	Fixed	UC/SCC	48	39 (81%)
			Normal	21	7 (33%)
Yu ST [27]	1993	Frozen	UC	53	30 (57%)
			Normal	8	0 (0%)
Agliano [34]	1994	Fixed	UC	46	23 (50%)
			Normal	10	0 (%)
Noel [36]	1994	Fixed	UC	75	2 (2.7%)
			normal	15	0 (0%)
Smetana [40]	1995	Frozen	UC	110	59 (54%)
			Normal	41	2 (4.9%)
LaRue [41]	1995	Frozen	UC	71	28 (39%)
			Normal	8	0 (0%)
Gazzaniga [53]	1998	Frozen	UC	35	11 (31%)
			Normal	10	0 (0%)
Tekin [56]	1999	Frozen	UC	42	2 (4.8%)
			Normal	10	0 (0%)
Fioriti [60]	2003	Frozen	UC	32	1 (3%)
			Normal	20	0 (0%)
Barghi [62]	2005	Fixed	UC	59	21 (35.6%)
			Normal	20	1 (5.0%)
Badawi [66]	2008	Frozen	UC/SCC	20	9 (45%)
			Normal	20	0 (0%)
Shigehara [69]	2011	Frozen/fixed	UC/SCC/AD	117	18 (15%)
			Normal	10	0 (0%)
Cai [70]	2011	Frozen	UC	78	27 (34.6%)
			Normal	59	6 (10.1%)
Berrada [74]	2013	Frozen	UC/AD	43	22 (52.4%)
			Normal	5	5 (100%)
Kim [75]	2014	Fixed	UC	35	6 (17.1%)
			Metaplasia	12	1 (8.3%)

HPV, human papillomavirus; UC, urothelial carcinoma; AD, adenocarcinoma; SCC, squamous cell carcinoma.

6. HPV-type distribution detected from bladder carcinoma

Although HPV types 16 and 18 were analyzed in majority of the previously conducted studies, a wide spectrum of HPV types were recently determined by the PCR method. Most of the HPV types detected from bladder carcinoma were high-risk ones. Type 16 was consistently among the most common types; type 18 was also detected with relative frequency. According to eight studies, type 18 was most frequently detected from bladder carcinoma [26,35,51,62,65,72,74,75]. In some previous studies on HPV prevalence based on urine samples, type 18 was often detected along with type 16 [11–13]. Therefore, HPV type 18 may infect the urothelial epithelium with relatively more ease than other types.

7. Relationship between HPV infection and pathological type or tumor grade of bladder carcinoma

Squamous cell carcinoma (SCC) is the most common histopathological type of cancer in cervix, oropharynx, anus, and vagina, which is thought to be strongly associated with HPV infection. Conversely, 90% of bladder cancer cases are urothelial carcinoma (UC), and the other 10% is SCC or adenocarcinoma. The HPV prevalence varied according to the histopathological types of bladder carcinoma.

Westenend et al. found no HPV infection in 16 SCCs of the bladder based on ISH analysis, and concluded that high-risk HPV types were found only in four of 105 (3.8%) SCCs of the bladder, by summarizing 17 previous reports [59]. Other previous studies also failed to find HPV infection in bladder SCC cases [28,59]. However, HPV was detected from UC in almost all of the studies, which supports the etiological role of HPV in the development of bladder

carcinoma, in contrast to cervical cancer, oropharyngeal cancer, and anal cancer. SCC of the bladder is thought to be caused by prolonged irritation by infection with certain microorganisms, use of indwelling catheters, urinary stones, or schistosomiasis. Thus, HPV infection may have little or no influence in the development of SCC of the bladder.

With regard to pathological grades of bladder carcinoma, there are some previous reports on the relationship between pathological grades and HPV detection. Tenti et al. has described that HPV prevalence in 79 samples of bladder carcinoma was 32.9%, and HPV infection was frequently found in low-grade (grade 1) tumors compared with high-grade tumors [44]. Badawi et al. also mentioned that HPV was detected in 44.4% of bladder carcinoma cases, which tended to be frequent in low-grade tumors [66]. Our previous study showed that HPV was positive in 38% of grade 1 (G1), 8.5% in grade 2 (G2), and 0% in grade 3 (G3) carcinomas, and that HPV-DNA was more frequently detected in low-grade carcinoma than in lesions of higher grades (G2 or G3) [69]. These findings are consistent with the fact that HPV is frequently detected in low-grade oropharyngeal carcinomas with good prognosis [78]. Conversely, another study investigated the prevalence of HPV among the bladder wash samples in the patients with bladder carcinoma, and found positive correlation between HPV-positive rate and the pathological grade [65]. However, there is possibility of contamination from other bladder or urethral sites, beside the tumor tissue, when using bladder wash samples in this study. Thus, further studies need to evaluate the relationship between HPV prevalence and pathological grade.

Conversely, the pathological grade differed according to the material settings in which the target samples were primary or recurrent. Furthermore, the number of samples has been limited as above, and further studies are required to reach a more definite conclusion. The pathological grade generally has a potential effect on the recuperation of the patients with bladder carcinoma. Thus, it is an interesting issue on the effect of HPV infection in the prognosis of patients with bladder carcinoma.

8. Findings on the surrogate genes expression in HPV-positive bladder carcinoma

In the carcinogenic process of low-grade non-invasive bladder cancer or high-grade invasive bladder cancer, two different biological pathways have been proposed. One pathway for low-grade cancer is involved in chromosome 9 allelic loss and higher p16 expression, whereas another pathway for high-grade invasive cancer is characterized by p53 mutation and lack of p16, Ras, or fibroblast growth factor receptor-3 (FGFR3) expression [79].

HPV-E6 protein and E7 are well known as oncogenic proteins. HPV-E6 contributes to the loss of function of p53, one of the main cancer-suppression genes, by ubiquitination of this gene and enhancement of proteasome activity. In addition, E6 protein also suppresses the transcription of p53 directly. As described above, some previous studies described the relationships between HPV infection and p53 expression in bladder carcinoma. Tenti et al. indicated that HPV was more frequently detected in low-grade tumors than in high-grade tumors in which mutations of p53 protein were commonly observed [44]. However, Moonen et al. found no correlation between HPV infection and p53 overexpression in high-grade tumors [65]. Kamel et al. also reported that no correlations between HPV positivity and p53 protein accumulation were observed in bladder carcinoma [37]. As other events related to the p53 gene are commonly observed in bladder carcinoma regardless of HPV detection, no definite conclusions on the relationship between p53 expression and HPV infection can be reached.

Moreover, it is well known that another oncogenic protein, HPV-E7, inactivates pRb, resulting in commencement of cell proliferation. P16-INK4a is the cancer suppression gene that suppresses inactivation of the Rb protein, and the loss or mutation of p16 expression is often a critical event in the progression of many carcinomas, including bladder carcinoma [80]. However, high levels of p16-INK4a expression are linked to HPV-E7 activity, and these molecules are strongly expressed in high-grade cervical intraepithelial neoplasia and cervical cancer. Further, p16-INK4a is known as a surrogate marker of HPV-E7 expression [81,82]. One study reported that high levels of p16-INK4a expression were observed in most HPV-positive bladder carcinomas, whereas p16-INK4a was rarely expressed in HPV-negative carcinomas, and significantly higher scores for p16-INK4a were demonstrated in HPV-positive tumors than in those negative for HPV by a scoring system for distribution of immunohistochemistry signals [69]. This finding suggests that the HPV-E7 protein was expressed in tumor tissue of the HPV-positive cases, and that HPV infection may be strongly associated with the development of bladder carcinoma. However, two studies have denied the potential correlation between p16-INK4a expression and HPV infection in bladder carcinoma [73,75]. Further studies are needed to clarify whether p16-INK4a can also be a surrogate marker of HPV-E7 expression in bladder carcinoma. Molecular studies are needed to clarify the mechanism of HPV carcinogenesis and to elucidate the etiological role of HPV infection in the development of bladder carcinoma.

9. The relationship between HPV-positive bladder carcinoma and cervical neoplasm risk

The information on the relationship between HPV-positive bladder carcinoma and cervical neoplasm risk has been extremely limited. Barghi et al. investigated the relationship between cervical dysplasia in women and the evidence of HPV infection in tissue specimens obtained from the bladders of their spouses [72]. High-risk HPV-DNA was detected in 24 (29.3%) men with bladder UC, and four these 24 men with HPV-positive bladder tumor had cervical dysplasia based on their Pap smear tests. However, no dysplasia was found in those women whose husbands had HPV-negative bladder tumors. Moreover, another study tried to determine the critical factors and etiological role of HPV infection in the development of female bladder tumor [83]. HPV-DNA was detected in five (6.0%) of 84 eligible patients, and two HPV-positive cases had a past history of cervical cancer. Interestingly, the same HPV type 16 was detected in the bladder tumor and cervical cancer in these two cases.

Since HPV is transmitted by sexual contact, it is relevant to know the risk of developing other HPV-induced cancers for the partners of men or women with any HPV-positive cancers, including cervical cancer or bladder carcinoma.

10. Conclusion

Many epidemiological studies have demonstrated that HPV infection is frequently transmitted through sexual contact of external genitalia, but it also affects the urinary tract, including the urethra and urinary bladder. Furthermore, some reports demonstrated the presence of some morphological changes of cells related to HPV infection and mild atypical cells, suspected to be intraneoplasia, in HPV-positive samples obtained from the urinary tract. According to the results of some clinical studies or meta-analysis, HPV infection is likely to have a certain etiological correlation with the development of bladder carcinoma, although its prevalence may vary by HPV type, study population, geographical region, histological type, detection methods, and among other

variables. However, since the HPV prevalence in bladder carcinoma greatly varied in previous studies, further case–control or large-scales studies are required to reach a more definite conclusion.

Conflict of interest

None.

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